REMARKS

Claims

Claims 3–6, 12–15 and 17 are currently under examination with claims 7–11, 16 and 18–21 withdrawn from consideration due to restriction/election. Claims 1–2 are cancelled without prejudice or disclaimer. Claim 22 is added by this paper.

Claim amendments

The claims have been amended according to conventional US practice.

Amended claim 1 is supported by the disclosure contained in, for example, the paragraph bridging pages 5 and 6 and page 7, lines 11–21 of the originally-filed specification. See, also instant claim 6.

Use claims 16, 18, and 20 have been amended to recite process claims, in conformance with conventional US practice.

New claim 22 recites the subject matter of claim 4 in independent form.

Applicants respectfully submit that the amendments presented herein do not raise new matter.

Claim objections

The Examiner is thanked for her careful reading of the claims. The objections, not specifically discussed herein, are moot in view of the amendments.

Rejection under 35 U.S.C. §112, ¶2

The contention that the instant claims "lack requisite structural features for the claimed composition" is respectfully traversed insofar as the primary structure of the wild-type Phl p 1 polypeptide was appreciated in the art before the filing date of the instant application. See, for example, page 3, lines 19–27 of Applicants' own specification and the disclosure contained in Petersen et al. (*J. Allergy Clin. Immunol.* 95, 987-994, 1995; PUBMED ID: 7751520). Based on this disclosure, a skilled artisan can readily obtain information pertaining to the polypeptide and/or polynucleotide sequence for wild-type Phl p 1. See, CITEXPLORE results which are enclosed herewith in Exhibit A. For example, it can be readily understood that UniProt accession No. Q40967 relates to *Phleum pretense* pollen allergen, while mRNA sequence has the EMBL accession No. Z27090 (formerly, PPRPHLP1X). Printouts of these sequences are enclosed

herewith for the Examiner's review.

The requirement that the claims explicitly recite sequence identifier number(s) of the polypeptides claimed herein is thus unnecessary. A skilled artisan can readily determine both the nature (i.e., mutant or wild-type) as well as the structure (i.e., amino acid sequence) of the rPhl p1 species claimed herein. See, *Capon v. Eshhar v. Dudas*, (Fed. Cir. 2005) 418 F.3d 1349, 76 U.S.P.Q.2d 1078 (discussed *infra*).

With respect to the alleged indefiniteness caused by the claim term "higher" and the rejection under §112, ¶2 based thereon, it is respectfully submitted that in view of the express knowledge of the wild-type Phl p 1 polypeptide sequence, coupled with a skilled worker's understanding of the structural characteristics of proteins, the metes and bounds of the claimed subject matter is well-understood by one of ordinary skill in the art. Withdrawal of the rejection is respectfully requested.

Rejoinder

Withdrawn claims 9–11 along with claims 16, 18, and 20 are drawn to a method of making/using the compound(s) and/or composition(s) of the instant invention and recite all the elements of Applicants' product claims. "If a product claim is found allowable, process claims that depend from or otherwise require all the limitations of the patentable product may be rejoined." See M.P.E.P. § 806.05.

Rejoinder thereof is therefore respectfully requested.

As to rejoinder of the method claims, the Examiner is cordially invited to revisit the descriptive portion of Applicants' specification directed to such embodiments. See, for example, the disclosure contained in the Examples. Applicants submit that in view of the totality of the disclosure contained in the specification regarding the activity of the claimed molecules, a skilled worker who is familiar with the techniques of immunotherapy can use routine techniques for making and using the claimed compounds/compositions in a manner recited in the claims. Thus, the statutory requirements under §101 and §112 are duly satisfied. Favorable action is earnestly solicited.

Rejection under 35 U.S.C. §102(b)

The contention that the subject matter of Applicants' claims 1–3, 5, 12–15 and 17 is anticipated by Focke (*FASEB Journal*, vol. 15, 2042-44, 2001) is respectfully traversed.

Under item 13, the Office Action alleges that Focke's disclosure of "non-allergenic Phl p1 derived synthetic peptide [fragments]" anticipates the subject matter of the instant invention. Applicants respectfully disagree. Focke merely disclose peptide fragments (28–31 amino acid residues) derived from Phl p1 which contain an additional Cys at amino acid position 212 or lower. See, Table 1 at page 15 of Focke et al. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, ¶1

Reconsideration of the rejections made in the office action of October 9, 2007 is respectfully requested.

The foregoing amendments render moot the written description rejection. The polypeptides are now claimed in terms of specific sequences. This is not to imply that the original claim scope was problematic under US law.

Enablement

At the outset, it is respectfully submitted that the lack of enablement rejection with respect to the variant of Phl p 1 is moot in view of the aforementioned arguments and/or amendments. With respect to variants of the claimed polypeptides, the PTO's contention is respectfully traversed. Applicants' specification, further in view of the art knowledge of Phl p 1 allergens and sequences (as substantiated by the references cited therein), provides a detailed description of the structure/activity of the claimed molecules. Structures (for example, amino acid sequences) of the claimed Phl p 1 species are recited in the instant sequence disclosure, further in view of the references cited in page 3 of the present specification. See, for example, the cDNA/polypeptide sequences disclosed in aforementioned reference by Petersen et al. It is now well-settled that a specification need not disclose, and preferably omits, what is well known to those skilled in the art when an application is filed (for example, with respect to the sequence of Phl p 1 species and/or variants thereof). See, e.g., *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). See, also, MPEP §2164.05(a). Indeed, the Federal Circuit found that an application, which failed to disclose the amino acid sequence of a claimed protein, was not deficient in the written description requirement, despite the fact that the undisclosed sequence was an essential part of the protein's description. See, *Capon v. Eshhar v. Dudas*, (Fed. Cir. 2005) 418 F.3d 1349, 76 U.S.P.Q.2d

1078. Likewise, in the instant application, the specification need not provide express guidance with respect to the sequence/domains in Phl p 1 species.

With respect to the variant sequences, reference is made to several art publications which exemplify the various methods and high level of skill in the art that existed at the time the present application was filed for identifying such molecules. These references provide ample evidence that routine protocols for epitope mapping were available and being employed in a variety of fields prior to and at the time of the filing of the present application. For example, Livingstone et al. (Ann. Rev. Immunol., vol. 5, 477-501, 1987) describe routine methods for identifying T cell epitope and provide models for predicting T cell epitopes in a protein on the basis of the primary sequence alone.

Moreover, synthesis of large arrays of unique peptides and use of such libraries for screening variants was routine in the art. For example, Geysen (PNAS, 81, 3998-4002. 1984) describes a method, subsequently referred to as "the pin method" or "the Pepscan method", which allows for the rapid, concurrent synthesis on polyethylene rods of hundreds of peptides of sufficient purify for ELISA assays. The screened peptides were mapped to eptitopes of foot-and mouth disease virus coat protein involved in antibody binding. Subsequent publications by the same author expressly account for the routineness of the procedure. "The current methodology requires only basic skills in organic chemistry, and can be used to synthesize more than 2000 peptides (hexapeptides) per 10 working day." Geysen et al. further state their group "presently tests about 4000 peptides each working day." See, Geysen et al., J. Immunol. Methods, 259-274, 1987. Van der Zee et al. (Eur. J. Immunol. 1989. 19:43-47) modified the Pepscan method so that the synthetic peptides could be released from the solid phase support, for direct use in T cell stimulation assays. Van der Zee used this modified technique to finely map a T-cell epitope in the mycobacterial 65 kDa heat shock protein. Likewise, Maeji et al. used the Pepscan methodology to map T cell epitopes of tetanus toxin (Maeji, N.J., Bray, A.M., Geysen, H.M., Multi-pin peptide synthesis strategy for T cell determinant analysis. J. of Immunol. Methods, 134, 23-33. 1990). Since 1993, the Pepscan technique has been made commercially available in kit form by Cambridge Research Biochemicals, Cambridge, UK. For example, Cason et al. used the Pepscan kit to map immunodominant epitopes of the bovine papillomavirus major (L1) capsid protein. (J. Gen. Virol., 74, 2669-2677, 1993). Likewise Ebner et al. utilized the Pepscan method to identify multiple T cell epitopes on the major birch pollen allergen Bet vl. (J. of Immunol., 150, No.3, 1047-1054. 1993).

In addition to the Pepscsan method, Houghten taught a method for synthesizing large

numbers of peptides on standard, amino acid resin that was sealed in packets (the "teabag" method). See, Houghten et al., PNAS, 82, 5131-5135, 1985. Using this method, the synthetic peptides could be easily cleaved from the resin allowing them to be used in liquid phase assays. Houghten used this method to simultaneously synthesize 248 different peptides from the influenza hemagglutinin protein (HA1), which were then used to map amino acids involved in the binding of anti-HA1 antibody. Houghten further states that his technique is simple and can be used to perform greater than 1000 syntheses simultaneously. Oftung et al. utilized the method of Houghten to map human T cell epitopes on the *Mycobacterium tuberculosis* 65-kilodalton protein antigen. (J Immunol., 141, 2749-54, 1988). As an alternative to protein synthesis, the generation of peptides from a known protein sequence could have been achieved by genetic manipulation of nucleic acid molecules encoding the protein of interest. Relevant techniques include, for example, the use of frequently and non-frequently cutting, restriction enzymes to generate fragments of a nucleic acid molecule encoding the protein of interest; the use of timed exonuclease III and/or Dnase I digestions of a nucleic acid molecule encoding the protein of interest; and the use of the polymerase chain reaction to generate precise fragments of the open reading frame encoding the protein of interest. All of these techniques were being employed at the time of filing. The methodology for performing the aforementioned techniques is further provided in rich detail in Methods in Molecular Biology, vol. 66, Epitope Mapping Protocols, 1996.

Not only was it possible to easily generate a multitude of peptides from a known protein, but techniques for high-volume screening of such fragments and peptides for T cell epitopes were clearly available. For instance, such screening could have been achieved by measuring T-cell proliferation in response to peptides in combination with antigen presenting cells. Many of the references already mentioned describe such assays. For example, the aforementioned Van der Zee, Ebner, Ofung, and Lamb references, all teach assays using 3^{H}-thymidine uptake by T cells as a way of measuring cell proliferation. Methods for assaying large number of samples, for example, employing a 96-well micro-plate, are also provided. It should be noted that plates having a higher density of wells (e.g., 384 wells) along with the use of automated readers capable of handling such platforms were available to the skilled worker as of the filing date of the instant application. In addition, several methodologies were being used to increase the efficiency of such screening and/or isolation of peptides of interest.

Accordingly, it is respectfully submitted that at the time the present application was filed, routine methods were available to screen for specific epitopes and to test the effects

contributed by the addition of each amino acid residue to a given epitope. For example, Focke et al. 2001 (cited in the Office Action) disclose Phi p 1 IgE eptitopes and the functional background of generating peptides with reduced IgE reactivity (for example the destruction or deletion of IgE epitopes). Also Schramm et al. 1999 (see specification on page 3, first paragraph) disclose mutated recombinant allergens in which IgE eptiopes are specifically deleted without impairing the T cell eptitopes, which are essential for therapy.

Claims directed to the pharmaceutical composition/vaccines

In the paragraphs bridging pages 5 and 6, the Office Action alleges that the pharmaceutical compositions are non-enabled. This contention is respectfully traversed.

At the outset, Applicants courteously submit that the Office Action fails to present any evidence which suggests the pharmaceutical compositions, as claimed herein, are not enabled. In the absence of such evidence, the rejection is deficient under controlling case law.

The burden is upon the Patent and Trademark Office to provide evidence shedding doubt that the invention can not be made and used as stated; see for example, *In re Marzocchi*, 439, F. 2d 220, 169 USPQ 367 (CCPA 1971). Moreover, Applicants' specification teaches that compounds of the present invention are useful for practicing the methods claimed herein. See, for example, page 5, lines 20-24 and page 20, lines 19-21 of the instant specification, as originally filed. In this regard, Applicants' specification expressly teaches that substituted hypoallergenic forms of allergens can be utilized as pharmaceutical compositions or vaccines. Rationale for the use of the compounds of the instant invention in the desensitization of a subject suffering from allergy is also provided. See, the paragraph bridging pages 1 and 2 of the specification, as originally filed.

In relation to an enabling disclosure on the utilization of Phl p 1 polypeptides as a pharmaceutical composition, the Examiner is courteously invited to review the disclosure contained in the Examples of the present application. For example, in Example 2 (page 17), Applicants' specification provides a disclosure of enzyme allegro sorbent test (EAST) for quantification of IgE binding to the claimed molecules. See, the disclosure in Fig. 3 and the description thereof at page 5 of the instant specification. Moreover, the disclosure in page 3, ¶1 of Applicants' specification and the cited Schramm reference expressly teach that the use of hypoallergenic peptide molecules, such as the rPhl p 1 variant polypeptide of the present invention, for therapy of allergic diseases was appreciated by one of ordinary skilled in the art. To this end, the Examiner is also cordially requested to review the "Immunization"

section of Focke et al and the immunoglobulin reactivity data provided in Figs. 5 and 6 and Tables 3–5 of the cited reference.

Thus it is respectfully submitted that the specification provides an enabling disclosure on the claimed allergenic properties of the Phl p1 polypeptides of the instant invention. Therefore, the specification's express teaching that the claimed compounds are pharmaceutically useful is clearly credible as required. The PTO's contentions regarding non-enablement based on the "unpredictability" and "lack of working examples" are especially weak in view of the detailed disclosure contained in Applicants' own specification and the state of the art before the earliest filing date of the instant application. Withdrawal of the rejection is respectfully requested.

Based on the aforementioned remarks and arguments, further in view of the amendments presented herein, it is respectfully submitted that Applicants' specification provides an enabling disclosure of what is claimed by the present invention. Withdrawal of the rejection under 35 U.S.C. §112, ¶1, is respectfully requested.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

No fees are believed to be due with this response; however, the Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

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